

**RECURRENT URINARY TRACT INFECTION IN THE FEMALE****\*Sameerah Sadiq Abdulsamad and Sahar Hatem Manhal**

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Iraq.**ABSTRACT**

Recurrent urinary tract infections (UTIs) have a significant effect on the quality of life of women affected by them. Continuous daily antibacterial prophylaxis (with trimethoprim 100mg or nitrofurantoin 50–100mg) reduces the risk of UTI in women while the antibacterial is being taken. However, the discomfort of a UTI needs to be weighed against the potential unwanted effects from the antibacterial therapy (vaginal and oral candidiasis, skin rash, nausea) and the risk of bacterial resistance to treatment, taking into account the preference of the woman. For some women, intermittent antibacterial therapy is an alternative: women with recurrent UTIs associated with sexual

intercourse who might be offered postcoital antibacterial prophylaxis; and compliant motivated patients in whom recurrent UTIs have been clearly documented who might prefer early acute self-treatment. Other options that are less likely to be effective but may be considered are vaginal estrogens for postmenopausal women or a daily intake of cranberry juice or cranberry product (the optimum daily dose of which has not been established). There is insufficient evidence to recommend lactobacillus probiotics, hyaluronic acid, and chondroitin, E. coli immunotherapy, acupuncture, or herbal medicine.

**KEYWORDS:** Urinary tract infection, female.**INTRODUCTION**

Women have a 50±70% lifetime risk of urinary tract infection (UTI) and a 20±30% chance of recurrent infection.<sup>[1]</sup> Most recurrences occur in the first 3 months following the initial infection<sup>[2]</sup>, with the number of recurrences experienced ranging from 0.3 to 7.6 a year; these recurrences often come in clusters. Obstetricians and Gynecologists as specialists in the care of women will see this problem almost on a daily basis, and therefore they require sound, up-

to-date knowledge of the assessment, treatment, and prevention of UTI (which has significant morbidity in both the pregnant and the non-pregnant female).

UTI is also a common sequel to urogenital pelvic surgery and an inevitable consequence of long-term urethral catheterization; the prevalence of bacteriuria increases 5±10% a day following catheter insertion.<sup>[4]</sup> Here, we review the diagnosis, pathophysiology, and management of recurrent UTI, with special reference to recent research developments which would be of interest to the practicing obstetrician/gynecologist.<sup>[3]</sup>

Risk factors associated with recurrent UTI in sexually active premenopausal women are the frequency of sexual intercourse, use of spermicides, age at first UTI (under 15 years indicates a greater risk) and history of UTI in the mother. After the menopause, risk factors include pelvic organ prolapse, incontinence, and post voiding residual urine. Before starting any prophylactic therapy, the infection needs treatment. UK guidelines recommend a 3-day course of trimethoprim (200mg twice daily) or nitro furanone (100mg twice daily).<sup>[4]</sup> Asymptomatic bacteriuria appears to play a protective role in preventing symptomatic recurrence and so should not be treated, except in pregnant women.

## **Background**

### **Diagnosis and assessment**

The diagnosis of UTI is usually made when symptoms of 'cystitis' are accompanied by significant bacteriuria. Symptoms of cystitis, such as painful or irrelative voiding, have a number of non-infective causes, that require accurate diagnosis. Symptoms of cystitis in women with previous confirmed UTI are a reliable guide to diagnosis: in one study of 172 patients, 94% had their suspected UTIs confirmed microbiologically.<sup>[5]</sup> Traditionally, significant bacteriuria was defined as more than 10<sup>5</sup> bacteria per ml freshly voided mid-stream urine.

This definition of significant bacteriuria with symptoms has been found to be too insensitive, up to 50% of infections being undiagnosed, so the lower bacteriuria rate of more than 10<sup>3</sup> organisms per ml is now generally accepted both in the non-pregnant female and in the pregnant, symptomatic female. Asymptomatic bacteriuria is defined on the basis of two consecutive, clean-voided urine specimens with more than 10<sup>5</sup> organisms per ml.<sup>[6]</sup>

Recurrent UTI may be caused by bacterial persistence of the original infecting bacteria, by reinfection with the same organism, or by infections with a different strain of bacteria. One recent study suggests that uropathogens may enter the urothelium, thus avoiding normal clearance during bladder emptying, and later cause recurrent UTI. Nevertheless, the majority of recurrent UTIs are caused by reinfection of rectal origin involving recolonization of the vaginal introitus and the lower urinary tract.<sup>[7]</sup>

Bacterial virulence factors are also important, especially when the urinary tract is otherwise structurally and functionally normal. Uropathy Gram-negative bacilli are present more frequently in the vaginal flora of women with recurrent UTI and are more likely to adhere to the urothelium in women with recurrent infections than in controls.<sup>[8]</sup> DNA fingerprinting of *Escherichia coli* strains has shown persistent vaginal and urinary tract colonization with the same *E. coli* strain in women with a history of UTIs. Lower local mucosal immunity with an inadequate secretory immunoglobulin A response to *E. coli* may also be important in the pathogenesis of recurrent UTIs.<sup>[9]</sup>

A small number of serogroups of *E. coli* cause a high proportion of recurrent infections because of the presence of virulence factors that increase bacterial adherence, toxin production (hemolysis) and serum resistance. Virulence genotypes have also been identified.<sup>[10]</sup> Recent reports of clonal groups of *E. coli* accounting for 51% of trimethoprim±sulpha me thoxazole-resistant *E. coli* UTI in a Californian cohort support the virulence theory and also raise the issue of ingestion of contaminated food products resulting in enteric colonization.

A detailed history is important for assessment and management. This should include the age at the time of the first infection, the number of previous UTIs, whether the lower or upper tract is involved, any history of diabetes or neurological disease, urinary tract calculi, and structural problems. The patient's voiding and bowel pattern, urine continence, and details of previous surgery, urinary instrumentation, and medications (including antibiotics, antihypertensive drugs, antidepressant therapy, diabetic therapy, and hormonal therapy) should be recorded. The sexual and contraception history (and any relationship to UTIs) and information about previous investigations performed and management strategies used (including the administration of antibiotics, urinary antiseptics or complementary medicines), allergies, and pregnancy (current or planned) should be elicited. A thorough general and neurological examination are essential. This should include assessment of the renal size and

the presence of any tenderness, whether the bladder is palpable, vaginal examination with assessment for atrophic vaginitis or prolapse, and urine analysis for glycosuria together with assessment (by means of a bladder scan) of the residual urine volume after voiding. Initial investigations required include a mid-stream urine sample for microscopy culture and sensitivity on one occasion. For frequent recurrent UTIs, in general, repeated urine cultures are not required except in cases of pregnancy, suspected complicated infections, or recent instrumentation or hospitalization. Testing is not cost-effective<sup>[11]</sup> and delays therapy. Empirical therapy of cystitis in women without urine culture is not associated with adverse outcomes and is cost-effective.

Episodic office urine testing (with leucoesterase strips) of samples collected prior to self-treatment can provide verification of the patient's diagnosis. Telephone-mediated management of women with suspected recurrent UTIs, with diagnosis and treatment by trained nursing staff, has been shown to be well tolerated and effective; outcomes are similar to those for office-based consultations.<sup>[12]</sup> This has also been shown to reduce the use of urine tests and increase the use of antibiotics, as recommended in guidelines.

Patient-initiated therapy for uncomplicated, recurrent UTIs based on self-diagnosis has also been shown to be well tolerated and effective, giving cure rates of 92% without significant adverse events. Structural and functional abnormalities of the urinary tract will also predispose women to recurrent UTI but are uncommon.<sup>[13]</sup> For this reason, the evaluation of women with recurrent UTI by using radiological imaging or cystoscopy is only warranted if indicated upon clinical assessment. Women with previous urogenital surgery may have a functional (impaired bladder emptying) or structural (suture and calculus).<sup>[14]</sup> abnormality causing recurrent UTI that is treatable. Women with persistent haematuria following UTI resolution should be investigated with cystoscopy and imaging.

### **Pregnancy**

UTI is the most common medical complication during pregnancy. Symptomatic UTI occurs in 1±2% pregnancies, while asymptomatic bacteriuria has been reported to vary at between 2 and 13%. Hormonal changes during pregnancy and pressure of the gravid uterus can impair bladder emptying and cause vesicoureteric reflux predisposing to lower and upper UTI. During pregnancy, UTIs are more common in women who are older, of higher parity, of lower socioeconomic status, have a past history of UTI, have an anatomical or functional urinary tract abnormality, or have the sickle cell trait or diabetes. Previously reported adverse

outcomes associated with UTIs, such as preterm labor and low fetal birth weight, hypertension, and early pregnancy loss, may have been overestimated.<sup>[15]</sup> Nevertheless, recent reports linking maternal UTI and neonatal mental retardation and cerebral palsy are causes of concern. Leviton and Gilles reported a strong association between Gram-negative bacteremia, maternal UTI during pregnancy, and fetal encephalopathy, and postulated that endotoxin was the factor most likely to be responsible. Grether and Nelson also found a significant association between maternal UTI during delivery and unexplained spastic cerebral palsy in the infant. In a study of pregnant women with UTIs in South Carolina, McDermott et al.<sup>[16]</sup> found that untreated maternal UTI in pregnancy was associated with a 22% increase in infant mental retardation and developmental delay relative to the infants of women with treated UTIs, and with a 31% increased risk relative to the infants of women without UTIs. If these risks are confirmed, this will further emphasize the importance of early diagnosis, effective treatment, and prevention of recurrence of UTIs during pregnancy.<sup>[17]</sup>

The choice of antibiotics for lower UTI during pregnancy and for women planning pregnancy has traditionally been the Food and Drug Administration category A and category B antimicrobial drugs (penicillin's and cephalosporin's). Sulphonamides may increase the risk of kernicterus in the neonate<sup>[18]</sup>, and trimethoprim (an antifolate agent), may interfere with normal neural tube development of the fetus in early pregnancy (though it is well tolerated in the second and third trimesters). Nitrofurantoin has the rare, but serious, a complication of neonatal hemolysis due to glucose-6-phosphate deficiency, but hemolytic disease in the newborn infant has not been reported. Nevertheless, some authorities are now recommending nitrofurantoin, trimethoprim or trimethoprim ±sulfa meth oxazole as the first-line treatment, because of their cost-effectiveness, relative safety, and low uropathogenic bacterial resistance.<sup>[19]</sup>

Three-day, short-course regimens are now recommended for the treatment of acute, uncomplicated cystitis during pregnancy, as in the non-pregnant state, because of their equal efficacy, better compliance, lower cost and lower levels of complications. Pregnant women with complicated UTI or who are at high risk of UTI recurrence should be given 7±10-day regimens. The high-risk group would include women with a history of recurrent UTI, women with pyelonephritis, or women who have unusual or resistant uropathogens. These women should be considered for long-term antibiotic prophylaxis during pregnancy.<sup>[20]</sup>

### Menopause and aging

Older women are more likely to get UTI and have a recurrence. Ikaheimo *et al.*<sup>[28]</sup> found that UTI recurrence in women over 55 was 53%, as opposed to 36% in younger women. Bacteriuria is present in 40% of elderly, non-institutionalized women and is the major cause of bacteremia.<sup>[21]</sup> Women over 60 have a 10±15% incidence of recurrent UTIs. Older women have a reduced in amatory and immunological status. They also have a higher incidence of diseases such as diabetes, a higher incidence of local urogenital factors (such as impaired bladder emptying and increased pelvic-or dysfunction causing urinary and fecal incontinence), and a higher incidence of genital prolapse.<sup>[22]</sup>

Raz *et al.*, in a case-controlled study of 149 healthy postmenopausal women with a history of recurrent UTI and 53 controls without a history of UTI, found that significant factors in the recurrent UTI group were urinary incontinence (41% versus 9% in controls;), the presence of cystocele (19% versus 0%), and residual urine after voiding (28% versus 2%). Also, a history of urogenital surgery was a significant risk factor for recurrent UTI. Another important aetiological factor in postmenopausal women is estrogen deficiency. Loss of oestrogenic hormones following the menopause results in atrophy of the urogenital tract and connective tissue. The epithelium of the urethra and vagina in well-oestrogenized women is stratified squamous epithelium, which changes to pseudostratified columnar and transitional epithelium in the proximal urethra and bladder. Estrogen stimulation causes proliferation of both urethral and vaginal epithelium.<sup>[23]</sup>

Oestrogen also stimulates the proliferation of lactobacilli by increasing intravaginal glycogen, which, in turn, reduces vaginal pH and vaginal colonization of uropathogens of rectal origin. Stamey and Sexton found that women with recurrent UTIs have signified- cantly higher colonization with *E. coli*, *Enterococcus faecalis*, *Proteus mirabilis* and *Klebsiella* than do women without a history of recurrent UTI. In a randomized, double-blind placebo-controlled study, Raz and Stamm studied 93 postmenopausal women each of whom had a history of recurrent UTI; it was found that intravaginal oestriol cream significantly reduced the incidence of UTI in the treatment group compared to the placebo group (0.5 versus 5.9 episodes per year; P50.001).<sup>[24]</sup>

Vaginal colonization by lactobacilli reappeared in 61% of the oestriol-treated group and in none of the placebo group. Colonization with Gram-negative bacteria decreased from 67% to 31% in the oestriol group and was unchanged with placebo. In another prospective

randomized study, Benness *et al.* compared oral oestriol (1 mg ovestin daily) and a placebo in 72 postmenopausal women with recurrent UTIs. After 6 months of treatment, the percentage of women who remained infection free was 43% in the oestriol-treated group and 49% in the placebo-treated group. The Heart and Oestrogen and Progesterone Replacement Study was a 4-year randomized trial to evaluate estrogen and progesterone therapy for the prevention of coronary heart disease in high-risk patients.<sup>[25]</sup>

A subgroup of 1525 incontinent women was randomly assigned to treatment with conjugated estrogen (0.625 mg) and medroxyprogesterone acetate (2.5 mg daily) or with a placebo; they were followed for a mean of 4.1 years. Interestingly, the oral estrogen/ progesterone group was associated with worsening urinary incontinence of both stress and urge types, and there was no significant difference in the number of UTIs (in the previous year) between the two groups.<sup>[26]</sup>

Therefore more research is required to study the role of exogenous estrogen replacement in postmenopausal women in the prevention of recurrent UTIs and pelvic-or dysfunction in postmenopausal women.

### **Management**

After a thorough clinical assessment, explanation and reassurance are important. Common myths should be dispelled. Underlying conditions should be treated, if possible, and women using diaphragms and spermicidal cream should consider using alternative forms of contraception. Asymptomatic bacteriuria is common, occurring in up to 40% of the institutionalized elderly, but is not associated with morbidity. Nevertheless, continence and bowel management, perineal hygiene, and hydration should be reinforced. In women with catheter-associated infection, catheter management should be reviewed; indwelling catheters should be removed, if possible, or at least changed. In diabetics, avoidance of hyperglycemia reduces UTI generally and postoperatively. For women with frequent, recurrent UTIs, three approaches to antibiotic therapy are available: patient-initiated therapy, postcoital therapy, or long-term prophylaxis. For many women with recurrent UTIs (either frequent or infrequent), episodic therapy prescribed after clinician consultation at the time of infection is commonly used. This has disadvantages in that it delays therapy, causing subsequent prolongation of symptoms, and is uneconomic.<sup>[27]</sup>

An alternative strategy is to provide an empirical antibiotic for 1 or 3 days, commencing at the onset of urinary symptoms. These women should have previously bacteriologically confirmed infection, be motivated and compliant with regard to medical instruction, and should report if symptoms persist after 4 h. For those women in whom infections are closely associated with the coital activity, postcoital antibiotic therapy can be used. Long-term prophylaxis can be used for women with very frequent infections, but this requires significant patient motivation. Antibiotic prophylaxis does not alter the natural history of recurrence, as 40±60% of women develop recurrent infections within 6 months of ceasing prophylaxis.<sup>[28]</sup>

The choice of antibiotic for the treatment of recurrent UTIs should be based on local antibiotic recommendations regarding local bacterial flora and resistance patterns, patient allergies and pregnancy status, cost-effectiveness, and simplicity of dose. Antibiotic resistance is increasing resulting in lower cure rates for cystitis and lower bacterial eradication for pyelonephritis. Risk factors for resistance include recent hospitalization and recent TMP-SMX use (odds ratio for TMP-SMX, 5.1; 95% confidence interval, 2.2±11.5).<sup>[29]</sup> Antibiotic options for women with recurrent UTIs include cotrimoxazole, trimethoprim, nitrofurantoin, amoxicillin ± clavulanate, cephalexin, and quinolones. The use of amoxicillin is now limited by increasing bacterial resistance. Beta-lactam antibiotics, including amoxicillin ± clavulanate, are less effective than cotrimoxazole or trimethoprim, even for a sensitive urinary isolate.<sup>[30]</sup> Cotrimoxazole is used less frequently in some countries because of the availability of trimethoprim, which is effective without having sulfur-related toxicity. Because of cost constraints and the possible development of resistance, quinolone antibiotics are recommended only for women with resistant organisms (e.g. *Pseudomonas*).<sup>[31]</sup> The choice of quinolone needs to be based on sensitivities and pharmacokinetics/pharmacodynamics. While uncomplicated cystitis could be treated with any quinolone, complicated infections require high urinary bactericidal activity (e.g. 500 mg Cipro oxacin twice daily or 500 mg levo oxacin daily, with increased doses for less-susceptible pathogens such as *Pseudomonas* spp.<sup>[32]</sup>

The best duration of therapy is debatable. Single-dose therapy is highly effective in women with acute cystitis<sup>[33]</sup>, but has a higher rate of recurrence and is less effective for recurrent infections in older women. Reviews of urinary tract therapy concluded that 3-day regimens of cotrimoxazole, b-lactams or fluoroquinolones were more effective than single-dose therapy.<sup>[34]</sup> Three-day therapy is also associated with a reduction in rectal flora ± the source of

infection in most women. More prolonged courses of cotrimoxazole are associated with increased adverse reactions with no benefit over three-day therapy.<sup>[35]</sup>

Beta-lactams are more effective if given for 5 days. In comparisons of the various regimens, cotrimoxazole (160/800 mg twice daily) was found to have a significantly higher cure rate than cefadroxil (500 mg twice daily), amoxicillin (500 mg three times daily) or nitrofurantoin (100 mg four times daily).<sup>[36]</sup> There are few data on short-course therapy in postmenopausal women; however, 200 mg ofloxacin given daily was more effective than 500 mg cephalexin given four times a day for 7 days. In general, for recurrent UTIs, a course of trimethoprim or cotrimoxazole for at least 3 days, or a 5-day course of  $\beta$ -lactams or nitrofurantoin, should be prescribed. In the elderly, there are few data on the appropriate duration of therapy, but a recent review recommended a 10-day course. In general, hospital-acquired pathogens are more resistant<sup>[37]</sup>, being associated with increased numbers of enterococci, resistant Gram-negative organisms, and staphylococci. A urine culture should be performed if the patient has recently been hospitalized.<sup>[38]</sup>

### **Hyaluronic acid and chondroitin**

Damage to the glycosaminoglycan layer lining the transitional epithelium of the human bladder may lead to direct exposure of the epithelial cells to urine components and to the possibility of bacterial adherence and infection.<sup>[39]</sup> Hyaluronic acid is a mucopolysaccharide widely found in the connective, epithelial and neural tissues. Chondroitin sulfate is another important structural component for bladder mucosal integrity. In theory, the application of these substances to the surface of the bladder could protect against infection. The combination was assessed in a double-blind randomized trial involving 57 women with recurrent cystitis (at least three symptomatic episodes with microbiological confirmation in the past year).<sup>[40]</sup>

Women received an installation in the bladder of 50mL of a sterile solution of hyaluronic acid (1.6%) plus chondroitin sulfate (2.0%) or placebo (50mL saline), which they were asked to retain for at least 2 hours, weekly for 4 weeks, then monthly for 5 months. Those who received the combination had fewer UTIs by the end of 1 year (a mean of 87% fewer vs. 10% fewer with placebo,  $p=0.0002$ ).

### Acupuncture

Two small randomized controlled trials evaluated the role of acupuncture compared with sham acupuncture or no treatment in the prophylaxis of recurrent UTIs.<sup>[41]</sup> In one, which involved 67 women, 85% were free of lower UTI during the 6-month observation period in the acupuncture group, compared with 58% in the sham group ( $p < 0.05$ ), and 36% in the control group ( $p < 0.01$ ). There were half as many episodes of lower UTI per person-half-year in the acupuncture group as in the sham group, and one third as many as in the control group ( $p < 0.05$ ).<sup>[42]</sup> In the other trial, involving 94 women, the difference in the number of women who were free of UTIs during the 6-month observation period (73% of women in the acupuncture group vs. 52% of women in the control group) was not statistically significant.<sup>[43]</sup>

### Herbs

Horseradish and nasturtium contain oils that are attributed with antibacterial properties. A double-blind randomized controlled trial involving 174 people (98% of whom were women) with recurrent UTIs assessed a tablet preparation containing horseradish root 80mg plus nasturtium 200mg compared with placebo, taken for 90 days. Patients were followed up for a further 90 days. When data were analyzed for all randomized patients the herbal preparation did not significantly reduce the number of UTIs compared with placebo.

In the elderly, there is increased toxicity with some antibiotics: nitrofurantoin is associated with pulmonary and neural toxicity, and cotrimoxazole is linked with blood dyscrasias. Drug interactions also need to be considered, e.g. interactions with the oral contraceptive pill in young women, and, in the elderly, interactions of cotrimoxazole with warfarin and methotrexate, and of euro-quinolones with iron, antacids, and theophylline. Morbidities such as vaginal candidiasis (with amoxicillin or amoxicillin-clavulanate, particularly in younger women) and tendonitis (with quinolones) also require consideration.<sup>[44]</sup>

Long-term prophylaxis should be considered for those women with three or more UTIs per year. The antibiotic choices for the prevention of UTIs with long-term prophylaxis include trimethoprim (100±150 mg note), cotrimoxazole (40/200 mg note), nitrofurantoin (50± 100 mg note), cephalexin (125±250 mg note) or nor<sup>-</sup>oxacin (200 mg note). Nitrofurantoin intermittently sterilizes the urine, and nor<sup>-</sup>oxacin and cotrimoxazole reduce uropathogens in fecal <sup>-</sup>ora.<sup>[51]</sup> Trimethoprim (100±150 mg note for 6±12 months) can reduce the rate of UTIs

from two or three episodes per year to 0.2 episodes per year. Long-term cotrimoxazole appears to be well tolerated and effective.<sup>[45]</sup>

For women with UTI related to sexual activity, postcoital prophylaxis can be implemented. Regimens include 40/200 mg cotrimoxazole, 50 mg nitrofurantoin, 125±250 mg cephalexin or 250 mg cinoxacin. For catheterized patients, long-term antibiotic therapy results in the selection of resistant organisms and should be avoided. The drinking of cranberry juice for the prevention of UTIs has received anecdotal support for many years, particularly in long-term care facilities. It reduces bacterial adherence and reduces bacteriuria. Three hundred milliliters of cranberry juice daily has been shown to be of benefit in a placebo-controlled trial, producing a 42% reduction in bacteriuria and pyuria, and a 27% reduction in persistent bacteriuria and pyuria.<sup>[46]</sup>

One study of the prevention of symptomatic infection showed that cranberry ± lingonberry juice reduced the UTI recurrence rate relative to that of subjects taking a placebo or lactobacilli. However, such studies are limited, and a randomized controlled trial is required. The introduction of *Lactobacillus*, either orally or vaginally, has not been shown to be effective in UTI prophylaxis. The identification of virulence genotypes among *E. coli* associated with recurrent UTIs also shows potential for the future development of vaccines for women with recurrent UTIs.<sup>[47]</sup>

## CONCLUSION

Recurrent UTIs pose a significant problem for women of all ages, but particularly for the elderly and women in long-term care facilities. A thorough understanding and assessment enable a targeted approach and appropriate management of the patient. Preventive strategies are effective, though further research is required in this area.

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